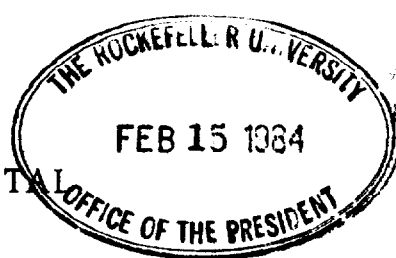




THE ROCKEFELLER UNIVERSITY HOSPITAL
1230 YORK AVENUE · NEW YORK, N.Y. 10021

Log ↓



PHYSICIAN-IN-CHIEF

14 February 1984

Dr. Joshua Lederberg
President
The Rockefeller University

Dear Josh:

Thank you for your memorandum of February 8th relating to the bilirubin problem - and for the other materials on this subject which you have sent earlier.

You know that if I don't promptly answer your inquiries I am not ignoring them, but I do try to answer them all in a batch when I settle down on weekends to catch up on correspondence and library work. But without going back into the literature, I can give you brief answers to this particular memorandum.

Free hemoglobin is a substrate for heme oxygenase in vitro but whether it serves directly as a substrate in vivo is not clear, but unlikely. Concerning the phagocyte question, we have had a 10-month study going on with the people at the Jackson Laboratories involving a strain of profoundly hemolytic (genetic basis) mice, who have received Sn-protoporphyrin in immense doses (100 $\mu\text{mol/kg}$ per week for 10 months). They show absolutely no toxicity; also nothing has happened to the spleen size where the red cell destruction is taking place; if anything, it may have diminished slightly in size. The liver size has not changed significantly either although we do not know the proportion of phagocytic versus hepatic cells in the liver at the present time. Since almost the entirety of heme metabolism takes place between the spleen (which has far more heme oxygenase than the liver) and the liver (which has much less enzyme but far more tissue), it is doubtful that we need to be concerned about alterations in phagocytic function elsewhere, particularly with single small doses of the metalloporphyrin. However the idea of studying this question is a good one, and we will talk to the cell biologists to see, in fact, whether the heme oxygenase which is in phagocytes is inhibited by tin-protoporphyrin, and how long the synthetic heme analogue survives in these cells (or how long the cells survive!).

Would the idea of a true competitive inhibitor substrate constitute the equivalent of a "targeted dose"? Wouldn't a chemical moving directly to an enzyme catalytic site be considered pretty good targeting? I don't think we need to put the stuff into phagocytes so much as we need to get it to the liver and spleen, particularly the latter which we appear to be able to do readily now as reflected in heme

Dr. Joshua Lederberg

14 February 1984

- 2 -

oxygenase (HO) activity and plasma bilirubin effects. The doses required for inhibition of HO are so tiny to begin with, I am not sure whether dropping the dose by even a factor of 10 would help, although that is always an advantage in this I guess. As I indicated earlier we have had an awful time trying to determine an LD-50 for this compound because we cannot get enough into solution to give to the baby rats, but the LD-50 dose is at least 100-fold greater than the dose required to suppress neonatal jaundice in the rat newborn. In our clinical studies the dose required to produce the effects which you have seen - and which we have chosen on an arbitrary basis although we have made some approximations based on the kinetics of heme and tin-protoporphyrin using human and rat spleen HO - have been between 1 and 2% of the dose required to suppress jaundice in the rat. I don't know the status of phagocytic function in the neonate. Estrogens are potent inducers of phagocytic activity and I assume that some residual effect of interuterine estrogens would suggest newborn transiently have increased phagocytic activity; and of course their spleens are larger which would add to this activity. I don't know how to calibrate drug dosage on human compared to animal cells in vitro, since I am not certain what human cells we can use. We do have a fine avian liver cell culture system for such a study, but nothing comparable of human origin. Concerning the inducibility of heme oxygenase in vitro - if you mean in vitro, to include tissue culture, the answer is "yes" the enzyme can be induced nicely in culture.

Finally, short-term treatment with tin-protoporphyrin does not affect P-450 in vivo in rat liver. I can imagine that on long-term treatment, the heme whose metabolism is inhibited by tin-protoporphyrin will ultimately suppress δ -aminolevulinate synthase, the rate-limiting enzyme of heme synthesis, and this in turn would then decrease the amount of P-450, since to some extent the content of P-450 is dependent upon the availability of heme as well as the capacity of the apoprotein synthesizing system. So far we have seen no effects on P-450. I'll get to your other inquiries later.

We have had an intense interest shown in this material by two major drug companies within the last couple of weeks; perhaps a conversation with Bill Griesar can bring you up-to-date on this. One of them has been Abbot-Ross Laboratories who have a powerful position in the neonatal field producing among other things, Similac. The other is Hoffmann-La Roche who have visited us three times so far and seem enraptured by the possibility that this compound might be used not only in the present population of patients receiving phototherapy, but in the much larger group of individuals with bilirubin levels over 10 just as a "preventive". In that respect I like their thinking, and would be glad

Dr. Joshua Lederberg

14 February 1984

- 3 -

to know if you have any preference of one company over the other - if both decide they want to take up an option on the compound. I have never seen the Arnold Rich paper - it having been published several years before I was born. I will however look it up.

The work is going extremely well, but one of these days I am going to need to drift off on a sabbatical some place because I am getting pretty weary for a lot of reasons - I get the sense I am not working as effectively as I would like to be. Is there any long-term assignment in the sun that you can put me on to?

With warmest regards.

Yours sincerely,

A handwritten signature in dark ink, appearing to be 'Kp' or 'Kappas', written in a cursive style.

Attallah Kappas, M.D.